REMARKS

In the Official Action dated November 29, 2010, Claims 28, 29 and 32-37 are pending. The following remarks address all outstanding objections and rejections. Favorable reconsideration of the pending claims is respectfully requested.

The Official Action alleges that the application fails to comply with the requirements of 37 CFR 1.821-1.825. In response, Applicants are submitting herewith a substitute copy of the sequence listing in accordance with 37 CFR 1.821(g). No new matter is introduced by this submission. In addition, the specification has been amended to reflect the proper sequence identification numbers, (SEQ ID), at the appropriate locations in the specification. Withdrawal of the objection to the specification is respectfully requested.

Claim 32 is objected to, based on an inadvertent typographical error. In response, Claim 32 has been amended to correct the chemical name of the dichlorophenyl moiety. No new matter has been added.

Claim 29 has been rejected under 35 U.S.C. §112, second paragraph as allegedly lacking antecedent support. In response, Applicants have amended Claim 29 to recite "...the CB1 receptor antagonist is...." to reflect proper antecedent basis. No new matter has been added.

Claims 28, 29 and 32-37 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Batkai et al. (Nature Medicine, Volume 7, No. 7, 2001, pp. 827-832) in view of Caprino et al., "Alpha-SMA Expression in Hepatic Stellate Cells and Quantitative Analysis of Hepatic Fibrosis in Cirrhosis and In Recurrent Chronic Hepatitis After Liver Transplantation", *Digestive and Liver Disease*, Vol. 37, pages 349-356 (2005). Batkai was previously raised as a reference under 35 U.S.C. §102(b). Now, the Examiner argues that "hepatic fibosis, the common final manifestiation of several chronic liver diseases is the result of a prominent accumulation of

extracellular matrix (ECM) materials and ultimately can lead to cirrhosis". Caprino et al., Abstract at lines 3-4 and 9-20. The Examiner alleges that hepatic fibrosis can serve as a precursor to cirrhosis.

Applicants respectfully submit that the Examiner has not even established a *prima facie* case of obvious. In the first instance, the secondary reference by Caprino et al. was published in 2005, after the priority date of the present application (i.e. March 9, 2004). Therefore, Caprino is not relevant prior art.

The present invention relates to a method of treating hepatic fibrosis in a mammal in need thereof which comprises administering a therapeutically effective amount of at least one CB1 receptor antagonist.

The present invention is not the mere discovery of a mechanism of action which would explain an effect already observed in the prior art. Quite to the contrary, the present invention constitutes a novel application of antagonists of the CB1 receptor based on the heretofore unappreciated and unsuggested novel technical effect: the reduction of fibrosis.

The existence of this novel technical effect leads to a spectrum of unique applications, which are distinct from those of the prior art.

In the present case, the invention provides, *inter alia,* that antagonists of the CB1 receptor reduce hepatic fibrosis and thereby can be used for the treatment of hepatic fibrosis which is an early stage of many forms of liver injury.

In contrast, Batkai et al. disclose that antagonists of the CB1 receptor may be used for decreasing the elevated mesenteric blood flow and portal pressure observed in cirrhosis, which is the end stage of many forms of liver injury. The prior art thus teaches that antagonists of the CB1 receptor reduce vasodilation in cirrhosis.

The use of antagonists of the CB1 receptor according to the present invention relies therefore on a distinct effect and targets a different population of patients, in order to treat a different spectrum of pathologies. Hepatic fibrosis is differentiate from cirrhosis and its treatment is patentably distinct.

Batkai et al. disclose the presence of CB1 receptor in endothelial cells isolated from hepatic arteries and their increased expression during cirrhosis. More particularly, Batkai et al. relate to advanced liver cirrhosis, namely the last step of cirrhosis, and to the activity of endocannabinoids as ligands of vascular CB1 receptors on the vasodilated state resulting from this advanced liver cirrhosis.

Nowhere does Batkai et al. teach or suggest that cirrhosis and the resulting vasodilated state are connected to hepatic fibrosis.

Batkai et al. mention on p. 830, left column, 2nd paragraph, that "*...SR141716A treatment was able to significantly reduce the markedly elevated mesenteric blood flow and portal venous pressure of the cirrhotic animals*".

Thus, all the results shown in Batkai et al. relate to altered blood flow during advanced liver cirrhosis and to the resulting increased blood pressure. Accordingly, Batkai et al. only pertains to a symptom of cirrhosis, namely a mechanism of action which leads to a severe alteration, even death, of the liver.

However, there is no suggestion of any link between hepatic fibrosis and cirrhosis in Batkai et al.

As stated on p. 831, end of left column:

"*The present findings suggest that this elusive mediator might be an endocannabinoïd acting at vascular CB1 receptors, and antagonists of these receptors might*

offer a therapeutic approach to the management of patients with advanced liver cirrhosis awaiting liver transplantation" (emphasis added).

This passage clearly shows that the use of CB1 antagonists in Batkai et al. is suggested to be used to address very late stage cirrhosis.

On the contrary, the subject-matter of present invention is to treat hepatic fibrosis at a very early stage, to avoid the type of treatment referred to in Batkai et al. Thus, Batkai et al. can, at best, be viewed as a clear teaching away from the claimed invention.

Notwithstanding the fact that Caprino is not even prior art, Applicants note that Caprino relates to evaluating the changes in distribution and percentage of alpha-smooth muscle actin-positive hepatic stellate cells and the correlation with the degree of the fibrosis in cirrhotic livers in patients with recurrent HCV (Hepatitis C Virus). Caprino specifically investigates the role of alpha-smooth muscle actin (SMA) as a marker of hepatic stellate cells (HSC) activation.

As mentioned in Caprino on top of page 350, left column, "*several studies have described that hepatic stellate cells (HSC) play a central role in the pathogenesis of fibrosis*". The results of these studies show that "*HSC activation is a key factor in the natural history of human HCV and HBV chronic liver disease and that it precedes fibrotic hepatic accumulation*".

Notably, Caprino does not teach or suggest treating hepatic fibrosis but only detecting markers of hepatic fibrosis. Caprino is drawn to methods of diagnosis generally, and is devoid of any appreciation of the claimed methodology.

On the contrary, the present invention addresses treating hepatic fibrosis by targeting CB1 receptor, as shown in the experiments involving CB1-defiicient mice and wild mice –(See example 2, p. 20-24). The results show that CB1-deficient mice which lack CB1 receptor do not develop liver fibrosis. Thus, Caprino does not teach or suggest any information on the

involvement of CB1 receptors which could cure the significant deficiencies of Batkai et al. Withdrawal of the rejection under 35 U.S.C. §103 is requested.

Wherefore, it is earnestly believed the instant application is in condition for allowance, passage to which is earnestly solicited.

Should the Examiner have any questions or wish to discuss any of the above or this case otherwise, they are invited to contact the undersigned as indicated.

Respectfully submitted,

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